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AMENDMENT UNDER 37 C.F.R. §1.111	
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Attorney Docket	STAN-128/S99-066
Confirmation No.	9147
First Named Inventor	Brian Haab
Application Number	09/550,303
Filing Date	04/14/2000
Group Art Unit	1655
Examiner Name	Betty J. Forman
Title	*Microarrays of Polypeptides*

Sir:

This amendment is responsive to the Office Action dated 12 December, 2001 for which a three-month period for response was given making this response due on or before March 12, 2002. A Petition for a Three-Month Extension of Time is submitted herewith, making this amendment due on or before June 12, 2002. Accordingly, this response is timely filed.

In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

I. AMENDMENTS

COPY OF PAPERS ORIGINALLY FILED

IN THE CLAIMS

Please amend claims 1, 10-16 and 18-19, cancel claims 8, 17 and 30, and add new claims 31-37 as follows:

1. (Amended) A method of forming a microarray of discrete polypeptide regions of claim 31, said method comprising,

(a) loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus,

(b) tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support, and

(c) repeating steps (a) and (b) until said microarray is formed.

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10. (Amended) A microarray of polypeptides of claim 31 produced by the method of:

(a) loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus,

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(b) tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support, and

(c) repeating steps (a) and (b) until said microarray is formed.

11. (Amended) The microarray of polypeptides according to Claim 10, wherein said microarray comprises 100 or more discrete regions of distinct polypeptide per cm^2 of solid support.

12. (Amended) The microarray of polypeptides according to Claim 10, wherein said microarray comprises 1000 or more discrete regions of distinct polypeptide per cm^2 of solid support.

13. (Amended) The microarray of polypeptides according to Claim 10, wherein said polypeptides are immunological receptors.

14. (Amended) The microarray of polypeptides according to Claim 13, wherein said immunological receptors are antibodies.

15. (Amended) The microarray of polypeptides according to Claim 10, wherein said polypeptides are antigens.

16. (Amended) The microarray of polypeptides according to Claim 10, wherein said planar solid support comprises a cationic film which binds said polypeptide.

18. (Amended) The microarray of polypeptides according to Claim 10, wherein said polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure.

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19. (Amended) A method of simultaneously detecting the presence of multiple protein-binding ligands in a sample, the method comprising:

contacting said sample with a microarray of polypeptides of claim 31;

washing said support free of unbound sample; and

detecting the presence of bound ligands.

31. (New) A microarray of discrete polypeptides on a planar solid support, wherein each polypeptide is of at least 50 amino acids in length and wherein said microarray comprises 100 or more discrete regions of distinct polypeptide per cm^2 of planar solid support.

32. (New) The microarray of claim 31, wherein said microarray comprises 1000 or more discrete regions of distinct polypeptide per cm^2 of planar solid support.

33. (New) The microarray of polypeptides according to Claim 31, wherein said polypeptides are immunological receptors.

34. (New) The microarray of polypeptides according to Claim 33, wherein said immunological receptors are antibodies.

35. (New) The microarray of polypeptides according to Claim 31, wherein said polypeptides are antigens.

36. (New) The microarray of polypeptides according to Claim 31, wherein said planar solid support comprises a cationic film which binds said polypeptide.

37. (New) The microarray of polypeptides according to Claim 31, wherein said polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure.

II. REMARKS

Formal Matters

Claims 10-16, 18 and 31-37 are pending after entry of the amendments set forth herein. Claims 1-7, 9 and 19-29 are pending but withdrawn from consideration.

Claims 10-18 were examined. Claims 10-18 were rejected. No claims were allowed.

Claims 1, 10-16 and 18-19 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to Claim 10 is found in Claims 17 and 19 as originally filed and throughout the specification, in particular at the following exemplary locations: page 17, line 5 and page 4, line 28. For clarity only, and at the suggestion of the Examiner, in Claim 10 line 7, "the surface" has been amended to "a surface", and in Claim 16, "capable of binding" has been amended to "which binds". Claims 11-16 and Claim 18 were amended to alter their dependencies. Accordingly, no new matter is added by these amendments. Claims 1, 10 and 19 have been altered to make them dependent on claim 31.

The amendments to claims 1, 10-16 and 18-19 relate solely to limitations in length of the amino acid sequences that are deposited onto to the microarray surface which result in distinguishing the instant claims over the disclosure in the cited prior art (albeit Applicants do not acquiesce to the propriety of the rejection as noted above), which disclosure is ineffective in enabling the production of bound sequences significantly longer than 10 amino acids as discussed below. While the instant specification expressly discloses 50 amino acids as preferable, one of ordinary skill in the art would clearly understand that a range of equivalents exists between the operable enablement of the reference and that of the instant claims. Applicants expressly do not intend to relinquish any subject matter relating to any other element of the claimed microarray.

Please replace Claims 1, 10-16 and 18-19 with the clean version provided above.

Support for new claims 31-37 is found in the specification, from page 8 to page 12 and claims 10-18 as originally filed. Support for the density of the microarrays of claims 31 and 32 is found on page 11, on lines 25-27.

Claim 8, 17 and 30 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Restriction requirement

The Office Action mailed June 6, 2001 set out a restriction requirement as follows:

> Group I: Claims 1-9, drawn to methods of forming a microarray of discrete polypeptides;
> Group II: Claims 10-18, drawn to microarrays of polypeptides; and
> Group III: Claims 19-30, drawn to methods of detection.

Applicants elected the invention of Group II, with traverse, and argued for the rejoinder of Group I with Group II.

Applicants further traverse the restriction on at least the grounds that the Examiner should, upon allowance of the microarray product claims, rejoin the claims to methods of use thereof and methods of making them which are of the same scope as the allowed product claims, specifically the claims of Group I (claims 1-9, drawn to a methods of forming a microarray of discrete polypeptides) and Group III (claims 19-30, drawn to a methods of using the polypeptide microarrays). See, e.g., the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

Applicants acknowledge that the microarrays of claim 10, and in particular the microarrays of claim 31 and those dependent thereon can be produced by another and materially different process; however, this does not prevent the Examiner from Examining the method claims presented, nor does it

render proper any subsequent refusal to rejoin and examine the claims to methods of making and using the elected products that are of the same scope as the product claims, once the product claims are found allowable.

Applicants further note that new product claims presented herein to microarrays of polypeptides should be assigned to Restriction Group II, which are "drawn to microarrays of polypeptides." Claims 1-9 correspond to methods of making microarrays of claim 31, from which they now depend, and claims 19-30 now depend from claim 31 as well. Rejoinder of the claims of Group I and III with the claims of Group II, upon allowance of claims of Group II, is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

The Office Action stated that Claims 10-18 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claiming the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection.

Claim 10 has been rejected assertedly because "surface" on line 7 lacks proper antecedent basis in the claim. Claim 10 has been amended to recite "a surface of a planar solid support" and later in the claim recites "the surface of the planar solid support". Thus amended Claim 10 provides proper antecedent support for "the surface of the planar solid support".

Claim 10, line 7 recites "to break the meniscus" and the Office Action asserts that there is no antecedent support for "the meniscus". However, Claim 10, line 5 recites "the solution in the channel forms *a meniscus*". As such the Applicants assert that there is antecedent support for "the meniscus" in line 7 of Claim 10, and the claim has not been amended.

Claims 11-18 are each rejected assertedly because of improper claim dependencies. The dependencies of Claims 11-18 have been amended according to the suggestions of the Examiner. As such, amended Claims 11-18 have proper claim dependencies.

Claim 16 is rejected for reciting "a cationic film capable of binding said polypeptide" because it is unclear whether the film binds the polypeptide. At the suggestion of the Examiner, Claim 16 has been amended, for clarification, to recite "a cationic film which binds said polypeptide".

Claim 17 is canceled, thus the rejection of this claim is moot.

Applicants submit that the rejection of Claims 10-16 and Claim 18 under 35 U.S.C. § 112 has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. § 102(b)

The Office Action stated that Claims 10-14 and 17 are rejected as being anticipated by Pirrung *et al.* (U.S. Patent No. 5,143,854, issued 1 September, 1992). Specifically the Office Action asserts that Pirrung discloses a microarray of polypeptides deposited at defined positions on a solid support. Applicants respectfully traverse the rejection.

The instant application claims, *inter alia,* a microarray of selected polypeptides of at least 50 residues in length, where the microarray is on a planar support. Each of the rejected claims recites that each of the polypeptides of the array is "at least 50 amino acids in length".

Pirrung assertedly discloses an array or polypeptides made by attaching photolabile groups to the surface of a substrate, exposing selected regions of the substrate to light to activate the regions, attaching an amino acid monomer with a photoremovable group to the activated region and repeating the steps of activation and attachment until polypeptides of desired lengths and sequence are synthesized. In order to demonstrate the operability of the invention, Pirrung synthesizes the polypeptides YGGFL, GGFL, PGGFL, and YPGGFL, and related polypeptides or approximately 5 amino acids in length, and uses antibodies specific to YGGFL to demonstrate that a polypeptide had been synthesized with the correct sequence. Pirrung assertedly further provides, on column 9, lines 20-65, a method for synthesis of longer peptides and states:

> "The process results in a substrate having a surface with a plurality of polymers of the following general formula:
>
> $$S\text{-}[L]\text{-}(M_i)\text{-}(M_j)\text{-}(M_k)\ldots(M_x)\text{-}[c]$$
>
> Where square brackets indicate optional groups and M_i to M_x indicates any sequence of monomers. The number of monomers could cover a wide variety of values, but in a preferred embodiment, they will range from 2-100."

The Office Action asserts that Pirrung therefore discloses an array of polypeptides of up to 100 residues in length, which anticipates an array of polypeptides of more than 50 residues in length, the claimed invention.

To constitute an anticipatory reference, the reference must contain an enabling disclosure.[1] A reference only contains an enabling disclosure if a person of ordinary skill could have combined the description of the invention in the reference with his own knowledge of the art to have placed himself, and thereby the public, in possession of the invention. The mere disclosure of a formula of a composition or sequence of words used to designate a composition, does not, in itself, anticipate the compound.[2] If the prior art fails to provide a method for producing the composition, and no method is known or obvious to one of skill in the art, then the reference does not place the composition in the possession of the public and therefore does not anticipate the claimed invention.[3] Applicants argue that Pirrung does not enable an array of more than 50 residues in length, and thus does not anticipate claimed invention.

The research article Fodor *et al* (*Science* 251:767-773, 1991), enclosed, is published after the filing date of the Pirrung application, is authored by the inventors of the Pirrung patent, and describes the invention claimed in the Pirrung patent exactly. The Fodor paper shows light directed synthesis of two pentapeptides YGGFL and PGGFL on the surface of a substrate, shows that the peptides have been correctly synthesized, and further shows a ten-step binary synthesis of peptides of a range of sizes, up to 10 amino acids in length. Fodor describes the invention claimed in the Pirrung patent in considerable detail.

Fodor, on page 771, second paragraph of the first column states: **"The net coupling yield *per cycle* in these experiments is typically between 85 and 95 percent."** and further recites, in reference 9, the rigorous methods that were used to derived these figures. Therefore, each time a residue is added to a growing polypeptide chain using this method, it is added with an efficiency of 85-95%. Pirrung recites

[1] *Chester v Miller* 15 U.S.P.Q. 2d at 1333 (Fed. Cir. 1990); *Titanium Metals Corp. of America v. Banner* 227 U.S.P.Q at 778 (Fed. Cir. 1985); *Scripps Clinic and Research Foundation v. Genentech* 18 U.S.P.Q.2d at 1001 (Fed. Cir. 1991).
[2] *In re Brown*, 141 U.S.P.Q 245 at 249 (C.C.P.A, 1964).
[3] See *In re Hoeksema* 158 U.S.P.Q. 596 at 601 (C.C.P.A. 1968).

that fidelity is an important consideration, and several controls must be placed on the arrays to determine whether a particular result is an artifact.

For the purposes of the following discussion, it will be assumed that the coupling efficiency of each cycle is 90%, the average of 85% and 95%. Using the above information, simple algebra teaches that the synthesis of a polypeptide using these methods becomes less and less efficient. For example, assuming the first amino acid is coupled to the substrate is 100% efficient, the synthesis of a two-mer polypeptide will be 90% efficient, the synthesis of a four-mer polypeptide will be 73% (0.9 x 0.9 x 0.9), the synthesis of a 10-mer polypeptide will be 34% (i.e. 0.9^9), the synthesis of a 20-mer polypeptide will be 13% (i.e. 0.9^{19}) efficient, the synthesis of a 35-mer polypeptide will be 2.5% (i.e. 0.9^{34}) efficient, and the synthesis of a 50-mer polypeptide will be 0.5% (i.e. 0.9^{49}) efficient. Thus, using an average of 90% coupling efficiency, if a 50-mer is synthesized using the method of Pirrung, only 0.5% of the polypeptides will have the correct sequence. In other words, synthesis of a 50-mer using the method of Pirrung will result in a heterogeneous mixture of polypeptides, only 5 molecules in a 1000 of which will have the correct sequence.

Even in the best case, where a 95% coupling efficiency at every step of the synthesis is achieved, a mere 7.7% (i.e. 7 polypeptides out of 100) of 50-mer polypeptides in an array will have the correct sequence. In the worst case, where an 85% coupling efficiency is achieved, only 0.03% (i.e. three polypeptides out of 10,000) will have the correct sequence.

At this level, the Pirrung method has ceased to be functional, and is no longer method for synthesizing a selected polypeptide onto a substrate. This effect may have been already demonstrated by the Pirrung inventors themselves in the Fodor paper, in which it is noted that no polypeptide of over 7 residues in length was highly bound by a specific antibody (page 771, second column, second paragraph), despite at least one of the polypeptides (e.g. peptide 21) having a sequence that *should have* bound to the antibody because it had an amino terminal YG. Peptide 21 is a 10-mer.

As such, the Pirrung reference, evidenced by the teachings of the Pirrung inventors in the Fodor paper does not contain an enabling method for the synthesis of selected polypeptide of at least 50 amino acids in length. Since Purring is non-enabling for methods for synthesizing polypeptides at least 50 residues in length it is also non-enabling for the composition made by the methods. As such, Pirrung

does not anticipate the rejected claim, which recite an array of polypeptides, where each polypeptide is of *at least* 50 amino acids in length.

Applicants submit that the rejection of Claims 10-14 and 17 under 35 U.S.C. § 102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. § 102(b)/103(a)

The Office Action stated that Claims 15 and 18 are anticipated under 35 U.S.C. § 102(b), or, in the alterative as made obvious under 35 U.S.C. § 103(a) over Pirrung (U.S. Patent No. 5,143,854). Specifically, the Office Action asserts that Pirrung discloses a microarray of antigens of the claimed invention, and a microarray of polypeptides that have retained their binding properties conferred by their the dimensional structures of the claimed invention. Applicants respectfully traverse the rejection.

The instant application claims, *inter alia,* a microarray of selected polypeptides of at least 50 residues in length, where the microarray is on a planar support. Each of the rejected claims recites that each of the polypeptides of the array is "at least 50 amino acids in length".

As demonstrated above, the Pirrung reference, evidenced by the teachings of the Pirrung inventors in the Fodor paper, does not contain an enabling method for the synthesis of selected polypeptide of at least 50 amino acids in length. Since Purring is non-enabling for methods for synthesizing polypeptides at least 50 residues in length it is also non-enabling for the composition made by the methods. As such, Pirrung does not anticipate Claims 15 and 18, which recite an array of polypeptide of at least 50 amino acids in length.

Applicants submit that the rejection of Claims 15 and 18 under 35 U.S.C. § 102(b) or 103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 10-15, 17 and 18 have been rejected under 35 U.S.C. § 103(a) as obvious over Beattie (U.S. Patent No. 5,843,767, filed April 10, 1996) for the asserted reason that Beattie, although using a different method to make the microarray, discloses a microarray of polypeptides deposited at defined positions on a solid support, which makes the claimed invention obvious. Applicants respectfully traverse the rejection.

The M.P.E.P. teaches at §1242 that:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Thus, in order for a proper *prima facie* case to be made, a reference or a combination of references must teach or suggest all of the claim limitations.

As will be demonstrated below, the reference cited by the Examiner does not teach or suggest each and every element of the claims as pending.

The instant application claims, *inter alia,* a microarray of selected polypeptides of at least 50 residues in length, where the microarray is on a planar support. Each of the rejected claims recites a "planar" support.

The Office Action asserts that Beattie discloses a microfabricated multi-welled substrate, and is characterized by discrete and isolated regions that extend through said substrate and terminate on the second surface of the substrate (i.e. the substrate contains at least one well with a perforated bottom) such that a sample can be applied to the well, and be transferred to the other side of the substrate during

the course of a binding reaction. It is also asserted that Beattie further recites immunochemical analyses of protein mixtures, epitope mapping, assay of receptor-ligand binding and other assays that clearly suggest that the substrate can comprise an array of polypeptides. The Office Action asserts that the claimed invention can be made using the methods and suggestions of Beattie, and thus the claimed invention is obvious in view of Beattie.

In order for the Beattie invention to work, the substrate onto which samples are applied must have wells (tapered or non-tapered) into which a sample is applied (shown very clearly in FIG. 1A, FIG. 2, FIG. 3, and FIG. 4 in the Beattie patent). After sample application, the sample is drawn through the porous bottom of the well, preferably under pressure, to the other side of the substrate. The well is necessary to keep the sample contained while is *en route* to the porous bottom or the well. As such, Beattie recites substrates that have wells, and teaches that wells are essential to the operation of the Beattie invention. Beattie does not teach or suggest that substrates that are planar.

As such, Beattie does not teach or suggest a "planar" substrate, an element of the claimed invention. Thus, each and every element of the claimed invention is not taught in the cited art. Since each and every element of the invention is not taught in the cited, this prong of the three prong test of *prima facie* obviousness has clearly not been met. Accordingly, Claims 10-15, 17 and 18 are not obvious under 35 U.S.C. §103(a) over Beattie and this rejection may be withdrawn.

Claim 16 is rejected under 35 U.S.C. § 103(a) as obvious over Beattie for the asserted reason that Beattie discloses a microarray of polypeptides deposited at defined positions on a solid support, which, when coupled with the cationic film and motivation of Van Ness (U.S. Patent No. 5,667,976), renders Claim 16 obvious to one of skill in the art.

Van Ness teaches methods for binding a polypeptide on a solid substrate, particularly a bead and a dipstick. Generally, Van Ness teaches process for covalently immobilizing a polypeptide or polynucleotide to a solid substrate, comprising a) treating a solid substrate with an alkylating agent, b) reacting the treated solid substrate with an amine-containing polymer in such a way that the polymer covalently coats the solid substrate, c) activating the polypeptide or polynucleotide with an agent such as cyanuric chloride, and d) conjugating the polypeptide or polynucleotide to the solid substrate surface.

Van Ness does not teach a microarray of polypeptides on the surface of a planar substrate, or provide suggestion that his methods or compositions can be used to construct a microarray of polypeptides on a surface of a planar substrate.

Since, as demonstrated above, neither Beattie nor Van Ness teach or suggest planar substrates, the combination of Beattie and Van Ness do not teach each and every limitation of the invention. As such, the instant invention cannot be obvious over the combination of Beattie and Van Ness.

Applicants submit that the rejection of Claims 16 under 35 U.S.C. § 103(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-128.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 11, 2002

By: James S Keddie

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